DOI:10.1111/irv.12080
www.influenzajournal.com



# Routes of influenza transmission

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Remarkably little is known definitively about the modes of influenza transmission. Thus, important health policy and infection control issues remain unresolved. These shortcomings have been exposed in national and international pandemic preparedness activities over recent years. Indeed, WHO, CDC, ECDC and the U.S. Institute of Medicine have prioritised understanding the modes of influenza transmission as a critical need for pandemic planning. Studying influenza transmission is difficult; seasonality, unpredictable attack rates, role of environmental parameters such as temperature and humidity, numbers of participants required and confounding variables all present considerable obstacles to the execution of definitive studies. A range of investigations performed to date have failed to provide definitive answers and key questions remain. Reasons for this include the fact that many studies have not sought to investigate routes of transmission as a primary objective (instead, they have evaluated specific interventions) and that fieldwork in natural settings, specifically assessing the dynamics and determinants of transmission between humans, has been limited. The available evidence suggests that all routes of transmission (droplet, aerosol and contact) have a role to play; their relative significance will depend on the set of circumstances acting at a given time. Dictating the process are factors related to the virus itself, the host and the environment.

**Keywords** Aerosol, contact, droplet, influenza, transmission.

*Please cite this paper as:* Killingley and Nguyen-Van-Tam (2013) Routes of influenza transmission. Influenza and Other Respiratory Viruses 7(Suppl. 2), 42–51.

## Introduction

Limited understanding of influenza transmission has been a frequent obstacle during the development of pandemic influenza infection prevention and mitigation strategies. The science is hotly debated, especially the relative importance of transmission via large droplets and droplet nuclei.[1,2] In the aftermath of the 2009 A (H1N1) pandemic, clarification of the relative importance of different modes of transmission is critical for the refinement of evidence-based infection control advice for healthcare settings, schools, workplaces and homes.

Transmission of an infectious disease is the process by which an infectious organism moves from one host to another and causes disease. There are many factors that contribute to and influence this process and to appreciate them one must first understand the basic pathophysiology of the underlying disease process.

Influenza replicates in epithelial cells throughout the respiratory tree (both upper and lower respiratory tract).[3] Human viruses preferentially bind to cell surface receptors (sialyloligosaccharides) terminated by a N-acetylsialic acid linked to galactose by an α(2,6)-linkage.[4] The predominance of these receptors in different tissues reflects the tropism seen, for example α(2,6) are found mainly in the human respiratory tract.[5] As a result, both virus entry and exit in humans occurs through the respiratory tract, that is, mouth and nose. Virus is released from an infected host during events such as coughing, sneezing and talking. An 'expiratory spray' of different sized particles in which virus travels is produced. Virus gains entry to a new host via inhalation and/or direct contact and/or indirect contact. From here, target epithelial cells can be reached. The potential of the conjunctivae to mediate transmission of human influenza viruses remains uncertain[6] although data from tropism experiments with pandemic H1N1[7] and outbreaks of avian H7 viruses in humans that are marked by conjunctivitis[8] confirm the presence of α(2,3) receptors in the eye. Furthermore, it has recently been shown that an aerosolised live attenuated virus can reach the nasopharynx via an ocular route.[9] There is very little evidence to suggest that the faecal-oral or waterborne route of transmission occurs in humans, in contrast to transmission that occurs amongst birds.[10,11]

Three routes of human influenza infection transmission are widely accepted:

- Droplets: these particles can deposit on mucous surfaces of the upper respiratory tract (URT) such as the mouth

and nose. They can be inhaled but are too large (>10 μm) to reach the lungs.
- Droplet nuclei (hereafter referred to as aerosols): these particles are small enough to be inhaled (<5 μm) and reach the lower respiratory tract (LRT). They may also deposit on surfaces in the URT.
- Contact transmission: particles are transferred to mucous membranes of the upper respiratory tract either directly or via a contaminated object or person, that is, indirectly.

For viruses to cause infection in new hosts, a number of prerequisites exist; (i) they must survive in the environment; (ii) they must reach target cells in a new host; and (iii) enough virus must reach target cells such that an infectious dose is achieved and infection initiated.

By considering the transmission pathways outlined above, it is evident that factors related to the virus, the environment and the host may all contribute to transmission (Figure 1). To formulate and implement effective influenza control measures such as personal hygiene, social distancing and infection control, it is critical to understand the above factors as each of these in turn can influence the route(s) of transmission that are active.

Nearly, a century has passed since the first studies of influenza transmission were conducted and many questions remain unanswered, for example;
- What is the relative significance of the different routes of influenza transmission?
- Do transmission routes differ in different settings?
- What is the extent and significance of virus deposition in the environment?
- What environmental factors influence transmission?
- What is the relative effectiveness of hand hygiene, surgical face masks (SFMs) and respirators in preventing transmission?
- What other interventions may be used to reduce transmission?
- How important is transmission from asymptomatic and pre-symptomatic individuals?

This article is a review of the biological and scientific determinants that contribute to an understanding of the routes of transmission that operate in humans. For each route, evidence for and against its significance is presented. It concludes by identifying ongoing research gaps.

## Evidence base

The evidence base on influenza transmission is largely derived from six categories of study. Each of these has been evaluated to see whether or not a significant role for each route of transmission is supported.

1. Studies assessing influenza virus deposition and survival in the environment that inform the biologic plausibility of the proposed routes of transmission
2. Studies examining the epidemiology of disease in closed or semi-closed settings
3. Non-pharmaceutical intervention studies
4. Human influenza challenge studies

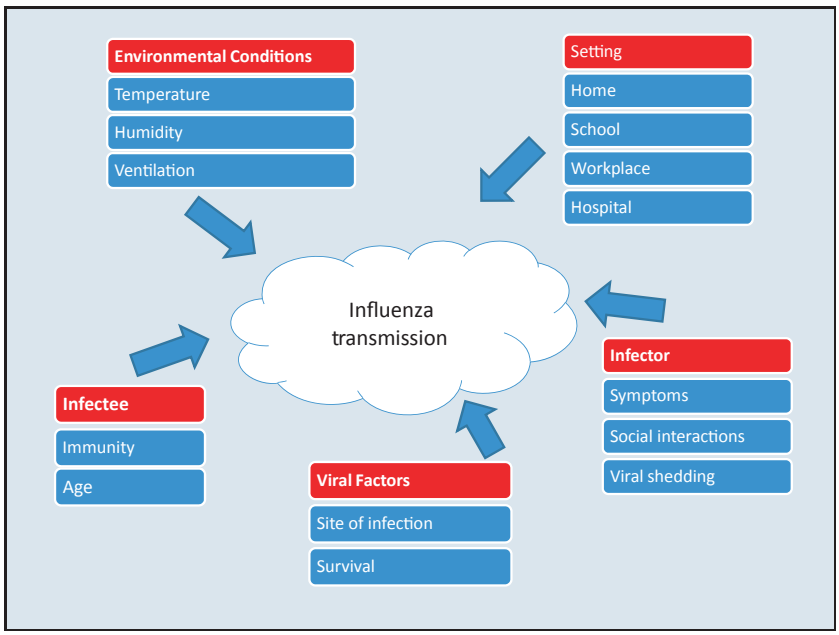


**Figure 1.** Factors that affect influenza transmission.

5. Animal models of transmission
6. Transmission modelling

## Studies assessing influenza virus deposition and survival in the environment that inform the biologic plausibility of the proposed routes of transmission

*Contact transmission*

There is sound evidence supporting influenza virus survival on fomites[12–14] and hands[12,15,16] for periods consistent with the possibility of onward transmission. Data regarding the likely survival time of virus deposited on surfaces are relatively heterogeneous and factors such as virus concentration of the inoculum, type of surface and temperature and humidity all affect virus survival. Thus, it is not possible to provide absolute numbers or ranges for survival times further than to say that estimates lie in the range of a few hours to several days. In general, the data support longer survival on hard (non-porous) surfaces than on softer (porous) items.

Few data demonstrate the recovery of viable virus from hands or surfaces contaminated by patients with influenza in natural settings.[17,18] Detecting virus by PCR is more sensitive, but whilst swab positive rates in some studies have been high (20–50%)[19,20], others have found lower rates 2–5%.[17,21,22] This might suggest that virus deposited by infected patients does not contaminate the vast majority of fomites in high titre. However, it might also reflect limitations in sampling efficiency, study designs and/or virological techniques.

Consideration of the transmission pathway for the indirect contact route does raise doubt about its plausibility. How likely is it that an infectious dose of virus can persist whilst passing along the transmission chain, infected secretions → (fingertips of infectors →) fomites → fingertips of infectees → mucous membranes → initiation of infection? No direct evidence exists to show that the contact route can mediate transmission, and the data currently available do not fully support the contact route of transmission playing a significant role in the spread of influenza.

*Droplet transmission*

Coughing and sneezing produce 'expiratory sprays' that consist of a range of particles lying on a size continuum from large particles (droplets) to small particles (aerosols) (reviewed by Nicas[23]). Aerobiological studies reveal that the vast majority of pathogens excreted in expiratory sprays are contained within droplets; this is related to the fact that droplets constitute 99% of the volume of an expiratory spray.[23–26] These particles behave ballistically and fall out of circulation within a few feet (range is proportional to size); they are potentially inhalable but cannot reach the LRT. Initiation of infection following the inhalation of particles is dependent on several factors such as infectious dose [thought to be higher in the URT than the LRT[2]], nose or mouth breathing, tidal volume, breathing rate and timing – so that an inspiratory breath in a susceptible contact occurs immediately after particle generation by an infected case. So, whilst the basic concept of droplet transmission may at first be readily accepted, the constraining factors mentioned have led some to consider it a rare event.[27]

*Aerosol transmission*

The majority of particles produced by an infected individual are <5 μm. Somewhat paradoxically, only a minor proportion of the total pathogens excreted will be contained within such particles, perhaps as low as 1%; this is a reflection of their relative volume.[25] By inference, the likelihood of infectious aerosol particles being produced is probably increased in patients who are shedding higher virus titres (e.g. those in the early days of illness, children, immunocompromised patients[28–31]), and data in support of this are emerging (Werner Bischoff 2012, Personal Communication).

Detecting the presence of influenza in the air is the first step in a chain of evidence needed to confirm that influenza viruses, emitted from an infected individual and existing as infectious aerosols, can initiate infection in a person exposed to them. The other steps in this sequence are (i) confirming that live virus is present and (ii) confirming that inhaled live virus can initiate infection.

Evidence backing up at least the potential for bioaerosol transmission of influenza is accumulating. Supporting evidence comes from the detection of influenza virus (by PCR) in the air of natural settings.[17,32–35] More recent work has shown that viable virus can be detected in exhaled breath[36] and cough samples from infected individuals[37] and that significant heterogeneity exists between individuals in the amount of virus emitted.[37] Influenza can survive in air for periods long enough to allow transmission (reviewed by Weber[6]). Overall investigators find that survival is prolonged (up to 24 hours) at low relative humidity.

## Studies examining the epidemiology of disease in closed or semi-closed settings

Most outbreak studies are inconclusive in determining the relative importance of different modes of influenza transmission. They suggest that most influenza transmission occurs at close range.[38–50] Although there is little epidemiological data to support long-range transmission of influenza, these data need to be placed in the context of the rapid diminution of concentrations of infectious aerosols as distance from the generating source increases. Thus, the absence of evidence for long-range transmission does not preclude a significant role for short-range spread via aerosol-sized particles, in some circumstances, at ranges normally or traditionally attributed to only ballistic-sized larger droplets.

Two reports describe circumstances favourable to aerosol transmission and its likely occurrence. One occurred aboard an aircraft that was grounded for 4.5 hours and had the ventilation system shut down[47], and the other took place on a hospital ward where the flow of air had been inadvertently altered.[48]

## Non-pharmaceutical intervention studies

A role for contact spread in the transmission of respiratory infections is supported by three systematic reviews[51–53] and one meta-analysis[54] that included data on hand hygiene (HH) to reduce the spread of acute respiratory infections. One review was specific to influenza[51], but in general these papers relate to acute respiratory infections as a whole as there is little organism-specific data. All reviews comment on the heterogeneity and often poor quality of studies performed, but all conclude that HH can reduce episodes of respiratory illness. More recently two studies have shown that HH interventions can reduce the incidence of influenza-like illness (ILI) and laboratory-confirmed influenza.[55,56]

Surgical face masks (SFMs) present a barrier to droplet transmission and by virtue of covering the mouth and nose can also reduce hand-to-face contact transmission. Respirators have the added potential benefit of reducing aerosol transmission as they can filter out droplet nuclei. A systematic review of the use of SFMs to reduce influenza transmission concluded that there are few data to endorse the wearing of a mask to prevent the wearer from becoming infected; there was in fact more evidence to suggest the use of a mask by an infected person can reduce transmission to others.[57] Studies comparing the effectiveness of SFMs and respirators are inconclusive to date and cannot easily be extrapolated to draw conclusions about modes of transmission.[58–60]

The non-pharmaceutical intervention studies performed to reduce influenza transmission are summarised in Table 1. A problem with using interventions to assess modes of transmission is that blocking one route still allows transmission to take place down other alternative (unblocked/open) routes. For example, if contact transmission is blocked by HH, transmission could still occur via droplets and aerosols making the interpretation of any risk reduction complex.

## Human influenza challenge studies

Humans can be experimentally infected with influenza following the instillation of drops intranasally[64] or by breathing aerosols.[65,66] In the study by Alford, 23 volunteers inhaled 10L of an H2N2 aerosol delivered via a facemask. The dose of virus delivered ranged between 1 and 126 $TCID_{50}$. Four volunteers developed clinical illness; virus was isolated from these and one other volunteer, whilst seroconversion was seen in seven including all those who exhibited illness. Noting limitations of the study design and making an assumption that only 60% of the aerosol load inhaled will reach the lower respiratory tract the study reports that half of the volunteers with very low pre-existing antibody titres were infected with 0.3–6 $TCID_{50}$. This is substantially lower than the infectious dose required for intranasal inoculation (100–1000 $TCID_{50}$)[67–69] and has led some to conclude that the LRT is the preferred site of infection and by implication (as only aerosols can reach it) that the aerosol route of transmission is important.[2,70] In addition, it has been suggested that natural infection may more closely resemble aerosol than intranasally initiated infection.[70]

## Animal models of transmission

The droplet and aerosol routes dominate in transmission experiments with animals (Table 2). Unfortunately, it is not possible to discriminate between them in most models[71–74] although it has been argued that the experimental methods described favour the operation of aerosol over droplet transmission.[75] Aerosol inoculation of ferrets has been found to simulate natural infection more closely than intranasal inoculation, and viable virus has been detected in exhaled aerosols.[76] The contact transmission route has appeared less significant in animal studies; however, interpretation of this in the context of human to human transmission is problematic because of the markedly different social and physical behaviours of humans compared with small mammals. There seems little doubt that some environmental factors such as temperature and humidity can affect transmission between animals.[77–79]

Through the use of animal models, a better understanding of the viral determinants of transmission is developing, although the variety and interplay of traits is complex; some seem to hinder transmission whilst others permit it through different routes. It is likely that viral properties (e.g. fitness for replication, receptor preferences) help determine infectiousness and modes of spread.[80,81] However, the extent to which all findings can be generalised to human transmission is uncertain and scientifically challengeable.

## Transmission modelling

A number of modelling scenarios have been constructed that combine defined physical dynamics with biologic processes to estimate outcomes (Table 3). Whilst most support the concept that all transmission routes can be important given the right circumstances, there appears to be divergence between those who conclude that droplet transmission is significant[83] and those who conclude it is less significant.[27,84,85] Despite droplet particles having high infectivity potential, it is likely that their inability to reach target cells, and data which reveal that the infectious dose in the URT is higher than the LRT[2] compromise this. Some models suggest a significant role for contact transmission[84–86] although

**Table 1.** Non-pharmaceutical intervention studies

| Study (year) | Study design | Study aim (*n* = subjects analysed) | Study setting/ randomisation unit | Study arms | Main findings |
|---|---|---|---|---|---|
| Talaat (2010)[55] | Cluster randomised controlled trial | Primary prevention (*n* = 44 451) | Schools | HH/Control | Significant reductions in ILI absenteeism and laboratory-confirmed influenza (A+B) |
| Stebbins (2011)[56] | Cluster randomised controlled trial | Primary prevention (*n* = 3360) | Schools | Hand + Respiratory hygiene/Control | Significant reductions in absenteeism and laboratory-confirmed influenza A |
| Aiello (2008)[54] | Cluster randomised controlled trial | Primary prevention (*n* = 1297) | University residences | SFM/HH + SFM/Control | No difference in cumulative incidence of ILI. During study weeks 4–6, weekly ILI incidence reduced in SFM + HH versus control |
| Cowling (2009)[61] | Cluster randomised controlled trial | Secondary prevention (*n* = 794) | Households (inc. index case) | HH/SFM + HH/Control | No difference in laboratory-confirmed secondary attack rates between study arms. Some effects seen if interventions (HH + SFM) implemented within 36 hours |
| MacIntyre (2009)[59] | Cluster randomised controlled trial | Secondary prevention (*n* = 286) | Households | SFM/respirator/Control | No difference in rate of ILI between arms. If compliant with mask use reductions in ILI seen with both masks |
| Larson (2010)[62] | Block randomised controlled trial | Primary and secondary prevention (*n* = 2788) | Households | HH/HH + SFM/Control | No difference in rates of clinical infection (upper respiratory infections and influenza). SFM use associated with reduced (SARs) |
| Simmerman (2011)[63] | Randomised controlled trial | Secondary prevention (*n* = 887) | Households | HH/SFM + HH/Control | No difference in laboratory-confirmed SAR between study arms. |
| Loeb (2009)[58] | Randomised controlled trial | Comparative non-inferiority (*n* = 446) | Healthcare workers (in hospitals) | SFM/Respirator | SFMs were non-inferior to respirators in relation to rates of laboratory-confirmed influenza |
| MacIntyre (2011)[60] | Cluster randomised controlled trial | Comparative efficacy (*n* = 1441) | Hospitals (healthcare workers) | SFM/Fit tested Respirator/ Non-fit tested respirator | Respirators were associated with an approximate halving of risk for all infection outcomes compared with SFMs, but after adjustment for clustering, the only significant finding was that non-fit-tested respirators were more protective against clinical respiratory infection |

HH, hand hygiene; ILI, influenza-like illness; LRT, lower respiratory tract; SFM, surgical face masks; URT, upper respiratory tract.

**Table 2.** Summary of animal studies

| Author (year) | Study/Investigation | Main findings |
|---|---|---|
| Andrewes (1941)[71] | Experimental infection in ferrets | Transmission occurred between ferrets housed in different cages and separated by distances that would arguably only permit aerosol spread |
| Schulman (1968)[74] | Experimental infection in mice | Transmission was demonstrated between mice housed in the same and separate cages, and the frequencies of transmitted infection were similar. One experiment allowed the ventilation in a cage housing donors and recipients to be altered; when ventilation was increased, infection rates decreased. These findings were interpreted as signifying that aerosol transmission was active |
| Lowen (2006)[72] | Transmission in guinea pigs | A human H3N2 virus was shown to replicate well in guinea pigs after intranasal inoculation and transmission from infected to recipient animals occurred when animals were housed together or in separate cages (side by side and separated by 91 cm) |
| Lowen (2007)[78] | Investigation of the effect of humidity and temperature on transmission in ferrets | Experiments on guinea pigs housed in an environmental chamber were conducted that only allowed for droplet or aerosol transmission. Low RH (20–30%) seemed to favour transmission whilst higher RH (80%) inhibited it. In another set of experiments, transmission occurred at low temperature (5°C) more frequently than higher temperatures (20 and 30°C) |
| Lowen (2008)[79] | Investigation of the effect of temperature on contact transmission in ferrets | Recipient guinea pigs were placed in cages that had housed infected ones with ambient temperatures of 20 and 30°C. Transmission was seen to occur equally at both temperatures; the authors suggest that whilst droplet and aerosol transmission is reduced by high temperatures, contact transmission is not (as virus is not released and therefore not exposed to the outside environmental) |
| Mubareka (2009)[73] | Routes of transmission in guinea pigs | The relative contributions of droplet/aerosol and fomite (contact) transmission were studied. Infected and recipient animals were placed in separate cages >80 cm above each other and transmissions occurred. However, when recipient animals were placed in the cages of infected animals (infected animals were removed but fomites were not) less infection transmission was seen |
| Gustin (2011)[76] | Comparison of aerosol and intranasal inoculation of ferrets | An aerosol inoculation system was devised. Aerosol inoculation caused a more natural influenza infection. Onward transmission was dependent on the level and duration of virus shedding. Viable virus was detected from infected ferrets in exhaled aerosols |
| Roberts (2012)[82] | Investigation into pre-symptomatic transmission | Transmission occurred via both contact and respiratory droplet exposure before the earliest symptoms developed. Furthermore, transmission did not temporally correlate with respiratory symptoms, such as coughs and sneezes, but rather with the peak viral titre in the nose |

**Table 3.** Modelling investigations

| Author (year) | Study/Investigation | Main Findings |
|---|---|---|
| Atkinson (2008)[27] | Model to quantify role of aerosol, contact and droplet routes based on a household scenario | They conclude that aerosol transmission is far more dominant than contact transmission and that droplet transmission is difficult to analyse without reliable data on how often people are in close (<1 m) contact, their relative heights and the directions of emitted sneezes and coughs |
| Nicas (2008)[86] | Investigation of the hand-to-face contact route of transmission | The scenario was a caregiver attending a sick family member in a bedroom for 30 minutes. An infection risk due to hand contact of 0.011% was generated |
| Nicas (2009)[84] | Model to quantify routes of transmission based on a scenario of visiting a patient's room | Important variables were considered to be (i) infectious doses and (ii) viral titres. When the URT/LRT infectious dose ratio is 3200:1 contact, aerosol and droplet routes all contribute substantially to infection risk. With rising viral titres, contact and aerosol become more significant. When the ability of virus to reach target cells is taken into account, aerosol transmission assumes dominance |
| Wagner (2009)[94] | Risk assessment of aerosol transmission aboard an airplane | The authors find that proximity and duration of exposure to the source and passenger density are important factors. Up to 17 infections could be caused during a 17-hour flight |
| Spicknall (2010)[85] | Model to quantify routes of transmission | The indirect contact mode of transmission appeared dominant. However, the authors explain that this is not necessarily the case in all settings. Of 10 000 model runs, indirect contact was dominant in 3079, respiratory in 121 and droplet in 66. Furthermore, considerable overlap is also seen where modes appear co-dominant, this occurred in 1969 sets |
| Teunis (2011)[83] | Model to quantify routes of transmission | Infectious dose data from influenza challenge studies are used in the construct of a model that simulates infection from a patient in a poorly ventilated room. Infection droplets and aerosols are approximately equal |

model outputs are highly dependent on estimates of infectious dose.

*Asymptomatic and pre-symptomatic transmission*

An important feature of infection in some individuals is that they shed virus but do not experience symptoms. This may happen early in the course of infection (pre-symptomatic) or exist throughout the course of an infection (asymptomatic). Such individuals may not seek treatment or self-isolate and therefore may be an important group. A recent ferret study has demonstrated that pre-symptomatic transmission does occur.[82] Amongst humans, models have typically assumed that asymptomatic or subclinical infections make up 33–50% of all infections[87,88] although empiric data obtained during the 2009 pandemic showed asymptomatic infection rates of 8–14%[89–91] with a subclinical rate of 25%.[90] Lau *et al.*[90] estimated that 1–8% of infectiousness occurs prior to illness onset. However, the amount and duration of viral shedding from asymptomatic patients can be low[90,92], and it remains to be shown that asymptomatic humans effectively transmit influenza.[93]

## Conclusion

### Contact

Contact transmission of influenza cannot be excluded; virus survival data show that it is biologically plausible. Its importance, however, is questioned by field data, although the scarcity and uncertain quality of those data are themselves problematic issues. More data from infected patients in natural settings are needed.

### Droplet

Droplet transmission is often assumed to be significant, probably because in epidemiologic investigations close proximity to the source patient is often noted to be necessary for transmission to occur; however, data generated from clinical studies to back this up are lacking. The issue is that close proximity spread does not adequately differentiate droplet transmission from other routes such as short-range aerosol transmission. Furthermore, despite the fact that the vast majority of virus released from an infected person during a cough or a sneeze is carried by droplets, with high infectious potential, droplets face two major challenges: (i) to reach their target cells and (ii) to satisfy the relatively high infectious dose needed to initiate infection in the URT (compared with the LRT).

### Aerosol

Aerobiological studies reveal that inhalable infectious particles ($\leq 5$ μm) can be produced by patients and that virus can remain viable (and therefore potentially infectious) in these particles long enough to permit infection transmission. A role for aerosol transmission from some infected

individuals in the absence of known aerosol-generating procedures cannot be ruled out, and a lack of evidence of long-range influenza transmission is not adequate evidence of absence of aerosol transmission at shorter distances. Of all the routes, it is perhaps aerosol transmission that has received most interest over recent years; evidence (albeit mainly indirect) in support of the importance of its overall contribution is increasing, but is still not definitive.

At present, the existing evidence on influenza transmission supports a potential role for all routes of transmission. Their relative significance will depend on the set of circumstances acting at a given time. Dictating the process are factors related to the virus itself, the host and the environment. Transmission can likely occur through multiple routes during the same 'event'; it is a dynamic and opportunistic process.

## Research needs relevant to policy and guidance

Further research is needed in the following areas to clarify policy and guidance issues[95,96]:

1. studies that further determine the importance of proximity (range) on human–human transmission;
2. studies that improve current understanding about the heterogeneity of virus shedding between individuals and within the same individuals over time (and in relation to symptoms);
3. studies that clarify the aerosol-generating potential of individual procedures in healthcare settings;
4. studies that clarify the relative contribution of contact, droplet and aerosol transmission;
5. studies that clarify the importance of human-human transmission arising from contact with infected, asymptomatic and infected pre-symptomatic individuals; and
6. studies that determine the effectiveness/efficacy of different types of masks, HH and combinations of personal protective measures for reducing transmission of influenza.

## Conclusion

At present, the existing evidence on influenza transmission supports a potential role for all routes of transmission. Their relative significance will depend on the set of circumstances acting at a given time. Dictating the process are factors related to the virus itself, the host and the environment. Transmission can likely occur through multiple routes during the same 'event'; it is a dynamic and opportunistic process.

## Conflict of interest

BK has no conflict of interests to declare. JSN-V-T has received research funding from GlaxoSmithKline and F. Hoffman-La Roche; and Astra-Zeneca within the last two years.

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